monotherapy. However, this comparison does not account for possible differences in costs when other factors are considered, such as route of administration (sunitinib is oral whereas interferon, bevacizumab, and temsirolimus are parenteral), number of clinic visits, toxicity checks, or supportive medications. A formal cost-effectiveness analysis could provide a more comprehensive comparison of cost differences between regimens.

At our centre, sunitinib is the preferred first-line treatment option for most patients with metastatic renal cell carcinoma, because of the availability of the drug as oral therapy, its high response rates according to studies with independent review, its safety profile, and its positive effect on health-related quality of life.[4,9] Nonetheless, the availability of alternative drugs is beneficial to patients, and allows for individual patients' characteristics and preferences.

Escudier and colleagues are to be commended for their phase III trial. The study supports the value of vascular endothelial growth factor blockade as a therapeutic approach to the treatment of metastatic renal cell carcinoma, and highlights the need for further research to define the optimum in the rapidly changing era of targeted therapy.

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Mechanical bowel preparation before colorectal surgery?

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Is mechanical bowel preparation of benefit to patients undergoing colorectal surgery? In today's *Lancet*, Caroline Contant and colleagues[1] report a randomised trial on more than 1400 patients who underwent colorectal surgery with or without this procedure. These investigators found that the occurrence of clinically significant anastomotic leaks was similar in both groups of patients (4·8% *vs* 5·4%, with and without the procedure, respectively; effect difference 0·6%, 95% CI −1·7 to 2·7%). They concluded that mechanical bowel preparation should not be done before elective colorectal surgery. In another trial, Jung co-workers[2] recently concluded similarly. They assessed more than 1300 patients and found no appreciable difference in clinical anastomotic leaks and intra-abdominal abscesses between patients who had the procedure and those who did not (2·6% *vs* 4·3%, effect difference 1·7%, 95% CI 0·7–2·7).

Sceptical empiricists, and perhaps some colorectal surgeons, might not be totally swayed by these studies. Although the absolute difference in leak rates was less than 1%, it amounts to a 20% relative difference between the groups. This issue is important because conscientious colorectal surgeons would regard the possibility of a 20% reduction in clinical leaks as being of great interest. If this figure is correct, it will be of interest to both patients and surgeons. A meta-analysis has shown that anastomotic leaks occurred more often after mechanical bowel preparation (5·1% *vs* 2·6%).[3] There were almost 2000 patients in the meta-analysis, which is less than the total number of patients in the two recent clinical trials (n=2776; table). These data, including both trials and the meta-analysis, probably add up to an interesting case-study for a biostatistician—to assess post-hoc power calculations versus the relative reliability of large-scale clinical trials and meta-analyses of several smaller studies.

Another major concern is the endpoints used by Contant[1] and Jung.[2] The complications of greatest importance are clinically evident anastomotic leaks and death. Diagnosis of anastomotic leakage can be subjective and difficult; clinically important leaks present either with diffuse peritonitis or localised signs associated with an abscess, and need some form of invasive treatment. Some other patients who do not recover properly have a phlegmon (an acute suppurative inflammation affecting subcutaneous connective tissue), but not all phlegmons progress to form an abscess. Leaks that are contained locally by the peritoneal defence mechanisms can also be asymptomatic, and both the recent trials argued that the subclinical leaks were not important. Yet even these leaks can be associated with long-term morbidity, such as anastomotic stricturing and poor bowel function.

In the Contant and Jung trials, abscesses were not counted as anastomotic leaks, but most intra-abdominal abscesses after colorectal resections are due to leaks, unless proven otherwise. The occurrence of abscesses in Contant and colleagues' study was significantly increased in the group not having mechanical bowel preparation compared with those who had the procedure (4·7% *vs* 2·2%; effect difference 2·4%, 95% CI 0·5 to 4·4). A similar outcome was also noted in the Jung paper, although statistical significance was not reached (1·7% *vs* 0·7%, respectively; table). If abscesses are analysed as if they were anastomotic leaks, then a review of these two large clinical trials shows a significant benefit in patients who had mechanical bowel preparation (effect difference 2·4%, 95% CI 1·5 to 3·3; table).

	Mechanical bowel preparation	No mechanical bowel preparation	Effect difference (95% CI)	p value (χ^2)
Jung et al[2]				
Leaks	13 (1·9%)	17 (2·6%)	0·7% (−0·9 to 2·3)	0·596
Abscesses	5 (0·7%)	11 (1·7%)	1·0% (0·4 to 1·6)	0·110
Contant et al[1]				
Leaks	32 (4·8%)	37 (5·4%)	0·6% (−1·7 to 2·9)	0·690
Abscesses	15 (2·2%)	32 (4·7%)	2·4% (0·5 to 4·4)	0·020
Combined trials[1,2]				
Leaks	45 (3·3%)	54 (4·0%)	0·7% (0 to 1·4)	0·437
Abscesses	20 (1·5%)	43 (3·2%)	1·7% (1·1 to 2·3)	0·003
Leaks and abscesses	65 (4·8%)	97 (7·2%)	2·4% (1·5 to 3·3)	0·027

Table: **Clinical trials of mechanical bowel preparation**

Another problem relates to standardisation of surgery in such trials. In a large prospective audit, anastomoses within the peritoneal cavity (including colorectal anastomoses above the pelvic peritoneal reflection) had a leak rate of 1·5% (19/1283) compared with 6·6% (21/316) for anastomoses below the pelvic peritoneal reflection.[4] Anastomoses below the peritoneal reflection might be protected by a covering stoma. Unfortunately, most clinical trials included in the meta-analyses excluded patients with ultra-low anterior resections (ie, anastomosis within 6 cm of the anal verge). Even in the two recent trials, Jung[2] excluded patients who might need a stoma and Contant and co-workers did not record information about the exact location of the colorectal anastomosis. Thus interpretation of the available clinical evidence in patients who had high-risk rectal anastomoses is difficult.

Those who scan papers and only read the bottom line will interpret the two recent trials, and the meta-analysis, as suggesting that it is unnecessary for patients undergoing elective colorectal surgery to have mechanical bowel preparation. That may well be true, but some doubts still need to be resolved, especially for patients undergoing low rectal anastomoses. Although evidence from trials favours not having mechanical bowel preparation, we should consider each case carefully, otherwise the chance of making an inappropriate decision exists, with great consequences for patients.

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We declare that we have no conflict of interest.

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ADRB2 polymorphisms and β_2 agonists

After the β-agonist controversy in the early 1990s, Liggett and colleagues' seminal work offered a possible pharmacogenetic explanation for patients with asthma who did not respond or even deteriorated when receiving inhaled β agonists.[1] Their in-vitro studies showed a functional relation between the cellular response to agonist and polymorphisms of the β_2-adrenoceptor (*ADRB2*) gene, especially those that confer aminoacid substitutions at positions 16 and 27 of the receptor protein. These studies provided a platform for investigation of not only whether heterogeneity in response to β_2 agonists might be genetically determined, but also whether susceptibility to adverse effects might be predicted on the basis of genotype. Subsequent clinical studies provided evidence that, at least with short-acting β_2 agonists, the Arg-16 polymorphism is indeed associated with adverse outcomes.[2,3]

In parallel with these developments, the world was moving on. Regular treatment with a short-acting β agonist was abandoned in favour of as-required dosing. Long-acting agents became available, and were soon established in guidelines as an adjunct to anti-inflammatory therapy. However, the concern simmered that, irrespective of pharmacogenetics, long-acting agents might still paradoxically contribute to asthma morbidity and even mortality.[4] The relation between *ADRB2* genotype and treatment outcomes with long-acting drugs needed to be explored further. Initial studies suggested a similar pattern of outcomes to those seen with short-acting β agonists. For example, in a small retrospective study, Wechsler and colleagues[5] reported that individuals who were homozygous for the Arg-16 polymorphism had an impaired response to salmeterol, irrespective of whether they were on inhaled steroids. Palmer and colleagues[6] reported that, in children taking salmeterol, the odds ratio for an asthma exacerbation during 6 months of follow-up was 3·4 in Arg-16 homozygotes compared with Gly-16 homozygotes. By contrast, in a small retrospective analysis of clinical trial data, no genotype-related adverse effects were identified.[7]

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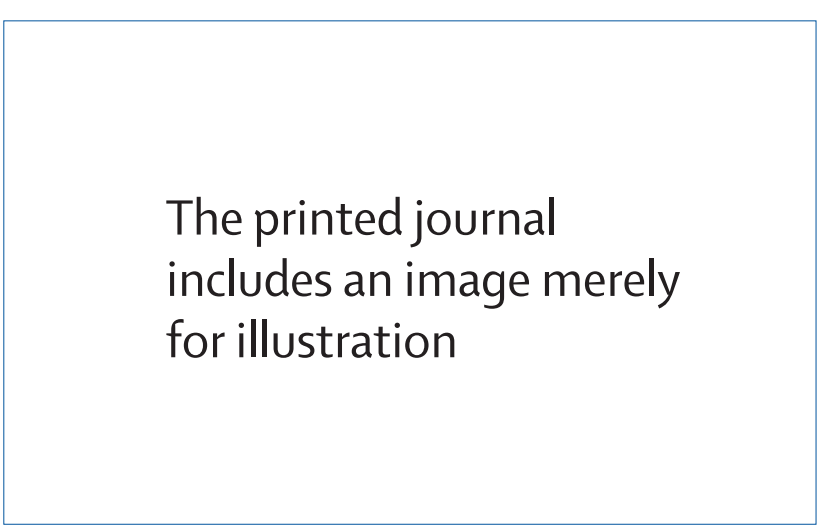
In today's *Lancet*, Eugene Bleecker and colleagues report the results of a much more substantial study, in 2650 participants with moderate asthma, of whom 430 had the Arg-16 genotype.[8] The results were clear. No association between treatment with either salmeterol or formoterol and clinical outcomes was identified after stratifying by *ADRB2* genotype or the relevant haplotypes. There was no evidence that the therapeutic response (increase in peak flows) was impaired in Arg-16 patients. These results were independent of the baseline bronchodilator response. More importantly, the frequency of exacerbations was no different between genotype subgroups, thus contrasting with what seems to happen with short-acting β agonists.[3]



β_2 adrenoreceptor, showing sites of genetic polymorphisms

Mechanical bowel preparation for elective colorectal surgery: a multicentre randomised trial

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Summary

Background **Mechanical bowel preparation is a common practice before elective colorectal surgery. We aimed to compare the rate of anastomotic leakage after elective colorectal resections and primary anastomoses between patients who did or did not have mechanical bowel preparation.**

Methods **We did a multicentre randomised non-inferiority study at 13 hospitals. We randomly assigned 1431 patients who were going to have elective colorectal surgery to either receive mechanical bowel preparation or not. Patients who did not have mechanical bowel preparation had a normal meal on the day before the operation. Those who did were given a fluid diet, and mechanical bowel preparation with either polyethylene glycol or sodium phosphate. The primary endpoint was anastomotic leakage, and the study was designed to test the hypothesis that patients who are given mechanical bowel preparation before colorectal surgery do not have a lower risk of anastomotic leakage than those who are not. The median follow-up was 24 days (IQR 17–34). We analysed patients who were treated as per protocol. This study is registered with ClinicalTrials.gov, number NCT00288496.**

Findings **77 patients were excluded: 46 who did not have a bowel resection; 21 because of missing outcome data; and 10 who withdrew, cancelled, or were excluded for other reasons. The rate of anastomotic leakage did not differ between both groups: 32/670 (4·8%) patients who had mechanical bowel preparation and 37/684 (5·4%) in those who did not (difference 0·6%, 95% CI −1·7% to 2·9%, p=0·69). Patients who had mechanical bowel preparation had fewer abscesses after anastomotic leakage than those who did not (2/670 [0·3%] *vs* 17/684 [2·5%], p=0·001). Other septic complications, fascia dehiscence, and mortality did not differ between groups.**

Interpretation **We advise that mechanical bowel preparation before elective colorectal surgery can safely be abandoned.**

Introduction

Symptomatic anastomotic leakage is the most important surgical complication after colorectal surgery and can cause morbidity and mortality. Mechanical bowel preparation has been regarded as an efficient strategy to prevent anastomotic leakage and septic complications. Observational data and expert opinions[1–4] have traditionally held that mechanical bowel preparation before colorectal surgery reduces faecal mass and bacterial count in the lumen. However, in the past few decades, the practice has been questioned.[5–10] In two studies, anastomotic leakage was more likely to occur in patients who had received mechanical bowel preparation before surgery.[7,8] However, these trials were underpowered, because of insufficient participants. We aimed to compare the outcome of elective colorectal resections with and without mechanical bowel preparation in terms of anastomotic leakage and other complications.

Methods

Study participants

Between April, 1998, and February, 2004, we enrolled patients at 13 participating hospitals (including nine teaching hospitals) in the Netherlands. The main criterion for inclusion was an indication for elective colorectal surgery with primary anastomosis. Patients were excluded if they had an acute laparotomy; had laparoscopic colorectal surgery; had a contraindication for the use of mechanical bowel preparation; had an a priori deviating ileal stoma; or were aged younger than 18 years. Surgeons in the participating hospitals enrolled patients in the study at the last visit before they were scheduled to have elective colorectal surgery. We obtained written informed consent from all patients.

Procedures

Enrolled patients were randomly assigned to either receive mechanical bowel preparation or not. A computer-generated randomisation list, stratified by centre, was prepared by the trial statistician (WCJH) at a central coordination centre. At the hospital where the trial was coordinated, patients were allocated to each intervention by means of numbered sealed envelopes that corresponded to the randomisation list; other centres were advised by telephone of the intervention allocated to each patient. The study was reviewed and approved by the ethics committees at participating hospitals.

Mechanical bowel preparation consisted of 2–4 L of polyethylene glycol bowel lavage solution in combination with bisacodyl (at 11 hospitals) or sodium phosphate solution (at two hospitals). Patients who had mechanical bowel preparation had a fluid diet (of beverages, yoghurt,

and soup) on the day before their operations. Patients who did not were allowed to have normal meals.

Before their operations, all patients were given intravenous antibiotic prophylaxis according to the guideline for prevention of surgical-site infection issued by the infectious diseases department of each hospital. All procedures were done by open laparotomy. Anastomoses were done according to the judgement of the surgeon.

The primary endpoint of the study was anastomotic leakage. Clinical suspicion based on persistent fever, abdominal pain, local or generalised peritonitis, or leucocytosis was followed by contrast radiography, CT scan, or laparotomy to substantiate the diagnosis. No effort was made to screen for asymptomatic leakage. Secondary endpoints were septic complications (wound infection, urinary infection, pneumonia, and intra-abdominal abscesses); fascia dehiscence; and death. Wound infection was regarded as mild if it manifested only with erythema or discharge of seroma, and severe if it was characterised by discharge of pus, wound necrosis, or wound dehiscence. We suspected urinary tract infections on the basis of clinical signs such as painful micturition, frequent micturition or urge, lower abdominal pain, or fever. The diagnosis of urinary infection was made for a urinary sample with a bacterial density of more than 10^2 per mL of urine for patients with symptoms and without a catheter, and of more than 10^5 per mL of urine for patients with a catheter. Clinical suspicion of pneumonia was based on cough, saliva, dyspnoea, or fever. We diagnosed pneumonia if radiography of the thorax showed infiltrative signs, and a saliva swab was positive for bacteria. The suspicion of an intra-abdominal abscess was based on clinical symptoms such as intermittent rise in temperature, persistent ileus, or abdominal pain. If an intra-abdominal abscess was suspected, we used CT or ultrasonography to investigate. This diagnosis could be also supported by perioperative findings. Fascia dehiscence was defined as receding of the abdominal fascia at the site or next to the fascia suture. The follow-up period was defined as the time from the operation until first outpatient visit, which usually took place 2 weeks after discharge from the hospital.

Statistical analysis

The study was designed to test the hypothesis that patients given no mechanical bowel preparation before colorectal surgery do not have a higher risk of anastomotic leakage than those given mechanical bowel preparation. We specified that for non-inferiority to apply, the upper limit of the two-sided 95% CI for the difference in anastomotic leakage rates (no mechanical bowel preparation group minus bowel preparation group) had to be less than 3%. We calculated that we would need a sample of 1400 patients to show with 80% probability that the upper limit of the 95% CI did not exceed the margin of 3%, assuming that the rate of anastomotic leakage in both groups was 5%.

We used the χ^2 test or Fisher's exact test to compare complication rates between groups, and the Mann-Whitney test to compare continuous or graded outcomes. The same tests were used in a univariate exploratory analysis to assess the risk of anastomotic leakage associated with: age, presence of hypertension, American Society of Anesthesiologists (ASA) classification, concurrent use of corticosteroids, preoperative radiation therapy, diabetes, coronary or peripheral ischaemic disease, smoking, body-mass index, indication for operation, type of anastomosis, technique of anastomosis (stapled versus handsewn), type of surgeon (length of training), and perioperative blood loss. We used multiple logistic regression to test risk factors simultaneously for any association with anastomotic failure. We regarded $p=0\cdot05$ as the limit of significance in all analyses. This study is registered with ClinicalTrials.gov, number NCT00288496.

Results

The figure shows the trial profile. Between April, 1998, and February, 2004, we enrolled 1431 patients. 77 patients were excluded from analysis of the primary endpoint: 46 (3·2%) because they did not have a bowel resection; 21 (1·5%) because we did not have outcome data; and 10 (0·7%) because they either withdrew consent, died, had an acute laparotomy, underwent surgery

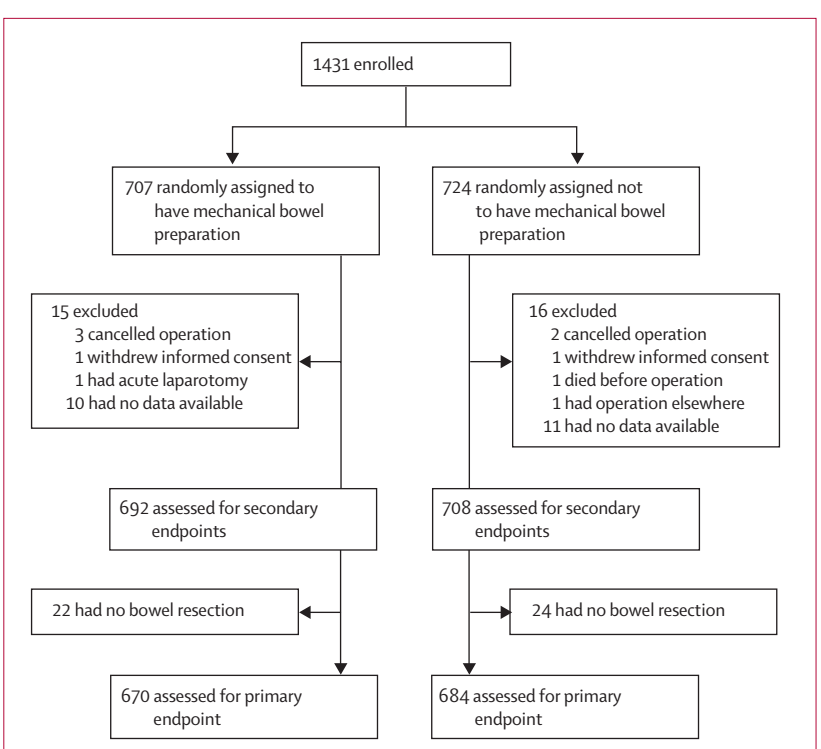

Figure: **Trial profile**

	Mechanical bowel preparation (n=670)	No mechanical bowel preparation (n=684)
Mechanical bowel preparation solution		
Polyethylene glycol	588 (88%)	602 (88%)
Sodium phosphate	82 (12%)	82 (12%)
Sex		
Female	333 (50%)	339 (50%)
Male	337 (50%)	345 (50%)
Mean age (years)	67 (13)	67(12)
ASA classification		
I	207 (31%)	212 (31%)
II	384 (57%)	386 (56%)
III	77 (12%)	83 (12%)
IV	2 (0·3%)	3 (0·4%)
Diabetes	66 (10%)	76 (11%)
Radiation	32 (5%)	22 (3%)
Corticosteroids	32 (5%)	27 (4%)
Coronary ischaemic disease	98 (15%)	109(16%)
Peripheral ischaemic disease	38 (6%)	36 (5%)
Smoking	165 (25%)	118 (17%)
Body-mass index		
≤25 kg/m²	329 (50%)	346 (52%)
>25 kg/m²	328 (50%)	319 (48%)
Indication for operation		
Colorectal cancer	487 (73%)	538 (79%)
Inflammatory bowel disease	122 (18%)	105 (15%)
Other*	61 (9%)	41 (6%)
Antibiotic prophylaxis		
Cefuroxim+metronidazole	320 (48%)	329 (48%)
Cefazolin+metronidazole	83 (12%)	80 (12%)
Cefamandole+metronidazole	70 (10%)	80 (12%)
Gentamycine+metronidazole	51 (8%)	56 (8%)
Amoxicillin-clavulanate	128 (19%)	130 (19%)
Others	19 (3%)	9 (1%)
Type of anastomosis		
Ileocolic	190 (28%)	209 (31%)
Colocolic	217 (31%)	237 (35%)
Colorectal	236 (34%)	213 (31%)
Other†	27 (4%)	25 (4%)
Technique of anastom osis I		
Stapled	207 (30%)	208 (30%)
Handsewn	444 (66%)	462 (68%)
Technique of anastomosis II		
End-to-end	291 (43%)	304 (46%)
Side-to-end	238 (37%)	239 (34%)
Side-to-side	93 (15%)	109 (17%)
End-to-side	19 (3%)	14 (2%)
Pouch	9 (1%)	5 (1%)

The number of patients for whom data were missing was less than 1% for all variables except body-mass index (n=34), technique of anastomosis I (n=75), and technique of anastomosis II (n=73). ASA=American Society of Anaesthesiologists. Data are number (%) or mean (SD).*Other reasons were radiation induced stenosis, endometriosis, and correction of Hartmann's procedure. †Coloanal anastomosis or ileorectal anastomosis.

Table 1: **Baseline characteristics of patients who had bowel resection**

elsewhere, or cancelled their operation. Baseline characteristics are shown in table 1. By chance, more patients who smoked and had inflammatory bowel disease were assigned to have mechanical bowel preparation.

Table 2 sets out postoperative complications, and shows that the rate of anastomotic leakage was about 5%, whether patients had mechanical bowel preparation or not (difference 0·6%, 95% CI –1·7% to 2·9%, p=0·69). The treatment effect did not differ between the 13 participating centres (OR homogeneity, p=0·67). 30 of the 69 cases of anastomotic leakage were verified by radiographic examination. 57 of the 69 patients had major anastomotic leakages that needed relaparotomy. The rate was about 4% in each group, whether patients had mechanical bowel preparation or not (difference 0·6%, 95% CI –1·6% to 2·8%, p=0·64). 6 patients in each group had minor anastomotic leakages that were treated conservatively. The median follow-up time for the 1354 patients who had bowel resection was 24 days (IQR 17–34).

Table 2 shows that fewer intra-abdominal abscesses happened after anastomotic leakage in those who had mechanical bowel preparation than in those who did not (p=0·001, 95% CI 0·9–3·4% for the difference). Of the 17 patients who did not have mechanical bowel preparation, and who developed intra-abdominal abscesses after anastomotic leakage, only three needed a relaparotomy for drainage of the abscess.

Rates of other septic complications, fascia dehiscence, and mortality did not differ between the two groups (table 2). Faecal contamination, number of days until resumption of a normal diet, and duration of hospital stay were similar in both groups (table 2). Results were similar when we analysed the 1400 patients for whom we had some outcome data, except that the rate of intra-abdominal abscesses did not differ between the groups (data not shown).

Exploratory univariate analysis of putative risk factors for anastomotic leakage showed that type of anastomosis (ie, ileocolic, colocolic, and colorectal anastomosis); ASA classification; and blood-loss during operation were associated with anastomotic leakage. These three associations remained significant in multivariate analysis (table 3). The two factors that were not well balanced between study groups (smoking and indication for operation), were not related to the primary outcome. Furthermore, the requirement for a stoma during the operation did not affect the leakage rate (table 3).

Discussion

Our study did not show any differences in anastomotic leakage between patients who were given preoperative mechanical bowel preparation before elective colorectal surgery and those who we not. Mortality and length of hospital stay were also similar in the two groups. However, patients who did not have mechanical bowel preparation had a slightly higher rate of intra-abdominal

	With mechanical bowel preparation† n=670	Without mechanical bowel preparation† n=684	Difference (95% CI)	p value
No postoperative complication	462 (69·0%)	452 (66·1%)	−2·9 (−7·9 to 2·1)	0·28
Anastomotic leakage	32 (4·8%)	37 (5·4%)	0·6 (−1·7 to 2·9)	0·69
Minor anastomotic leakage	6 (0·9%)	6 (0·9%)	0·0 (−1·0 to 1·0)	1·0
Major anastomotic leakage	26 (3·9%)	31 (4·5%)	0·6 (−1·6 to 2·8)	0·64
Wound infection	90 (13·4%)	96 (14·0%)	0·6 (−3·2 to 4·4)	0·82
Mild wound infection	49 (7·3%)	51 (7·4%)	0·1 (−2·7 to 2·9)	1·0
Severe wound infection	41 (6·1%)	45 (6·6%)	0·4 (−2·2 to 3·0)	0·83
Fascia dehiscence	19 (2·8%)	16 (2·3%)	−0·5 (−2·2 to 1·2)	0·69
Urinary tract infection	71 (10·6%)	70 (10·2%)	−0·4 (−3·6 to 2·9)	0·90
Pneumonia	39 (5·8%)	51 (7·5%)	1·6 (−1·0 to 4·3)	0·27
Intra-abdominal abscess	15 (2·2%)	32 (4·7%)	2·4 (0·5 to 4·4)	0·02
Abscess without anastomotic leakage	13 (1·9%)	15 (2·2%)	0·3 (−1·3 to 1·8)	0·85
Abscess with anastomotic leakage	2 (0·3%)	17 (2·5%)	2·2 (0·9 to 3·4)	0·001
Secondary intervention	58 (8·7%)	58 (8·5%)	−0·2 (−3·2 to 2·7)	0·99
Deaths	20 (3·0%)	26 (3·8%)	0·8 (−1·1 to 2·7)	0·50
Faecal contamination*	..	..	..	0·42
Clean contaminated	389 (58·1%)	380 (55·8%)	−2·3 (−7·6 to 2·9)	0·41
Contaminated	250 (37·4%)	276 (40·5%)	3·2 (−2·0 to 8·4)	0·26
Dirty	30 (4·5%)	25 (3·7%)	−0·8 (−2·9 to 1·3)	0·54
Operation time (min)	120 (90–150)	120 (90–144)	0·0 (−5·0 to 5·0)	0·48
Resumption of normal diet (days)	6 (4–8)	6 (4–8)	0·0 (−0·4 to 0·4)	0·91
Hospital stay (days)†	10 (8–14)	10 (8–13)	0·0 (−1·0 to 1·0)	0·40

Data are number (%) or median (IQR) unless otherwise specified. The number of patients for whom data were missing was less than 1% for all variables except for days until resumption of a normal diet (n=31) and hospital stay (n=29). *Clean contaminated=colon resection with minimal spill; contaminated=colon resection with severe spill of bowel contents, no pus; and dirty=intraperitoneal pus or bowel perforation. †Excluding postoperative deaths.

Table 2: **Postoperative complications, surgery data, and hospital stay for the 1354 patients who had bowel resections**

abscesses after anastomotic leakage. We did not regard the very low rate of abscesses to be of major clinical importance; abscesses did not influence the number of reinterventions, length of hospital stay, or mortality.

Efficient mechanical bowel preparation is generally supposed to help to prevent infectious complications after colorectal surgery. Theoretically, this procedure diminishes faecal load in the bowel and prevents disruption of the anastomosis by reduction of faecal impaction at the site of the anastomosis. Therefore, the risks of faecal contamination or infection of the peritoneal cavity and the abdominal wound are thought to be decreased. However, mechanical bowel preparation liquefies solid faeces, which could increase the risk of intraoperative spillage of contaminant.[5,11] Although some investigators believe that mechanical bowel preparation can reduce the bacterial load in the bowel, the large number of microorganisms in the digestive tract makes this almost impossible.[7,12] Mechanical bowel preparation has been shown to have potentially negative side-effects in terms of bacterial translocation,[13,14] electrolyte disturbance,[15–18] and discomfort to patients.[15,19–21] Despite these drawbacks, mechanical bowel preparation is still commonly practised in colorectal surgery, without evidence from randomised trials that it decreases complication rates in patients.[6–9,22]

Of the three published meta-analyses, the first showed that in three trials, with 497 patients, those who had mechanical bowel preparation had a significantly greater rate of wound infection than those who did not.[23] The second meta-analysis showed that in nine trials, with 1592 patients, mechanical bowel preparation was associated with a higher rate of anastomotic leakage, although wound infection and other complications did not differ between groups.[24] The third meta-analysis showed that in seven trials, with 1454 patients, those who had mechanical bowel preparation were significantly more likely to have anastomotic leakage.[25] Only one recent study has reported an increased risk of anastomotic leakage in patients who had colorectal resections after mechanical bowel preparation with a single phosphate enema compared with oral polyethylene glycol.[21] Mortality was higher in the oral polyethylene glycol group, but neither septic complications nor length of hospital stay differed between groups. After submission, we learned of another randomised trial of mechanical bowel preparation for elective colonic resection, in which the results paralleled ours.[26]

Multivariate analysis showed that ASA classification, type of anastomosis, and blood loss during operation were independent risk factors for anastomotic leakage. A possible explanation for risk associated with loss of blood

	Leakage rate	Odds ratio (OR)	95% CI	Multivariate analysis p values	Univariate analysis p values
Mechanical bowel preparation					
No	37/684 (5·4%)	1·0*	..	..	..
Yes	32/670 (4·8%)	0·81	0·48–1·34	0·42	0·69
ASA classification					
I	15/419 (3·6%)	1·0*	..	..	..
II	35/770 (4·5%)	1·33	0·71–2·47	0·37	..
III/IV	19/165 (11·5%)	3·83	1·87–7·84	0·0002	0·001‡
Type of anastomosis					
Ileocolic	12/399 (3·0%)	1·0*	..	..	..
Colocolic	23/454 (5·1%)	1·56	0·74–3·29	0·24	0·007§
Colorectal	32/449 (7·1%)	2·14	1·05–4·35	0·04	..
Other	2/52 (3·8%)	0·93	0·18–4·91	0·93	..
Operation indication					
Carcinoma	48/1025 (4·7%)	1·0*	..	..	..
Inflammatory bowel disease	14/227 (6·2%)	1·22	0·64–2·34	0·55	0·46¶
Other	7/102 (6·9%)	1·60	0·66–3·86	0·30	..
Smoking					
No	51/1066 (4·8%)	1·0*	..	..	..
Yes	18/283 (6·4%)	1·32	0·73–2·36	0·36	0·36
Blood loss					
<median†	22/664 (3·3%)	1·0*	..	..	..
≥median†	47/677 (6·9%)	1·93	1·12–3·32	0·02	0·004
Diverting stoma peroperatively					
No	63/1257 (5·0%)	1·0*	..	..	..
Yes	6/97 (6·2%)	0·99	0·38–2·59	0·99	0·79

Data are number (%), unless otherwise specified. ASA=American Society of Anaesthesiologists. *Reference category. †Median blood loss was 400 mL. ‡p value for trend. §p value for trend, excluding "other" types of anastomosis. ¶Overall p value.

Table 3: **Anastomotic leakage rates, according to various factors and results of multivariate analysis for the 1354 patients who had bowel resection**

is that decreased oxygen delivery at the anastomotic site due to anaemia might compromise anastomotic healing and therefore cause anastomotic leakage. Golub and colleagues[27] reported that a perioperative transfusion of more than two units of blood was independently associated with leakage, and suggested that the immunosuppressive effect of blood transfusions might have a role.

Our trial had several limitations. First, observers were not blinded to whether a patient had mechanical bowel preparation or not. However, since the number of surgical interventions for severe leakages did not differ between groups, the lack of double blinding probably did not cause bias. Second, we did not register all eligible patients who could potentially have been enrolled. However, because the characteristics of the patients in our study (table 1) corresponded closely to those of patients in the three published meta-analyses, we do not think that the external validity of our study was compromised by this omission.

Third, we used two different oral regimes for mechanical bowel preparation, since two hospitals had switched from use of polyethylene glycol to sodium phosphate for mechanical bowel preparation, on the basis of a report that these substances were equally effective and safe.[19] Our analysis showed that neither the difference in the rate of anastomotic leakage nor the difference in overall complication rate varied according to which type of mechanical bowel preparation was used.

Fourth, we did not record the exact height of anastomosis below the pelvic verge. Anastomotic leakage has been studied in relation to patient characteristics (such as malnutrition, body-mass index, cardiovascular disease, steroid use, smoking, alcohol abuse, and preoperative pelvic irradiation) and to surgery (level of anastomosis, operating time, perioperative blood transfusion, ASA classification, and intraoperative contamination of the operative field). The factor most consistently shown to predict leakage is a low rectal anastomosis.[27] Two recent randomised studies advised that patients undergoing elective anterior resections that were low or very low, should have mechanical bowel preparation because of a high risk of anastomotic leakage in extraperitoneal anastomosis.[28,29] However this advice was not based on solid evidence, since one study excluded extraperitoneal anastomosis[28] and the other only included 79 patients with a (low) anterior resection.[29] Platell and colleagues[21] studied 294 patients, 60% of whom had a low anterior resection. All anastomoses under the pelvic verge were radiologically assessed for leakage, whereas intra-abdominal anastomoses were only assessed if clinically indicated.[21] Although radiological assessment of anastomotic leakage did not differ between patients who did and did not have mechanical bowel preparation, both clinically relevant anastomotic leakage and severe anastomotic leaks were more common in the enema group.[21] In our study, 449 patients underwent a colorectal anastomosis below the level of the peritoneal verge. In this subgroup, we noted no differences with regard to anastomotic leakage or septic complications, whether patients had mechanical bowel preparation or not (data not shown).

Last, although we only analysed 1354 patients, statistical power was not greatly reduced because the resulting confidence interval for the primary endpoint was sufficiently narrow to exclude a relevant difference. Therefore, the conclusion that elective colorectal surgery can be safely done without mechanical bowel preparation is justified. In view of possible disadvantages of this practice, patient discomfort, and the absence of clinical value, we advise that mechanical bowel preparation before elective colorectal surgery should be abandoned.

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Transport policy is food policy

We endorse the call for fair and sustainable solutions to tackle the causes of global food insecurity (April 26, p 1389),[1] but argue for greater recognition of the importance of reducing the demand for transportation fuel in resolving the struggle for energy between people and cars.

Petrol tanks and stomachs were competing well before biofuels were proposed to tackle climate change. Motorised transport is more than 95% oil-dependent and accounts for almost half of world oil use.[2] Because oil is a key agricultural input, demand for transportation fuel affects food prices. Increased car use also contributes to rising food prices by promoting obesity which, for the reasons outlined below, increases the global demand for food.

We estimate that a population of 1 billion people with a stable mean body-mass index (BMI) of 24·5 kg/m² consumes an average 6·5 MJ of food energy per person per day to maintain basal metabolic rate, and a further 4 MJ per person per day for activities of daily living. An obese population of 1 billion people with a stable mean BMI of 29·0 kg/m² would require an average 7 MJ of food energy per person per day to maintain basal metabolic rate, and 5·4 MJ per person per day for activities of daily living (calculations available from the authors). Compared with the normal weight population, the obese population consumes 18% more food energy. Additionally, more transportation fuel energy will be used to transport the increased mass of the obese population, which will increase even further if, as is likely, the overweight people in response to their increased body mass choose to walk less and drive more.[3]

Urban transport policies that promote walking and cycling would reduce food prices by reducing the global demand for oil, and promotion of a normal distribution of BMI would reduce the global demand for, and thus the price of, food. Decreased car use would reduce greenhouse gas emissions and thus the need for biofuels, and increased physical activity levels, would reduce injury risk and air pollution, improving population health.

Transport policy is food policy and the importance of sustainable transport must not be overlooked.

We declare that we have no conflict of interest.

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Preoperative bowel preparation

Caroline Contant and colleagues' randomised trial of 1431 patients undergoing elective colorectal surgery (Dec 22, p 2112)[1] represents a milestone in the discussion concerning preoperative bowel preparation. Even though the rate of intra-abdominal abscesses was slightly increased in the group not undergoing bowel preparation, the general incidence was low (4·7% *vs* 2·2%; p=0·02). All other endpoints including mortality, length of hospital stay, and reintervention rate showed no significant difference between the groups. Contant and colleagues' conclusion was that preoperative bowel preparation can safely be abandoned.

This view was questioned by Cameron Platell and John Hall in the accompanying Comment (p 2073).[2] Unfortunately, and in line with the traditional point of view, they oversimplify the problem by narrowing it down to surgical problems around anastomotic leakage. They ignore an increasing body of evidence indicating that bowel preparation is harmful itself.

Besides substantially reduced patient comfort, this invasive procedure has been shown to cause severe side-effects such as electrolyte or acid-base imbalances and dehydration.[3] The corresponding liberal fluid infusion, usually done to re-establish the reduced intravascular volume, intensifies these disturbances and causes tissue oedema.[4] This problem prolongs wound healing and bowel function recovery time and increases reintervention rate, hospital stay, mortality, and the incidence of severe cardiopulmonary complications.[5]

There are several good reasons to question the necessity of preoperative bowel preparation. Hopefully the intriguing work of Contant and colleagues will help to extend the worldwide discussion on preoperative bowel preparation beyond abscess rates or the stability of enteral anastomoses, to achieve a real improvement in patients' outcomes.

We declare that we have no conflict of interest.

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